desirability of exercising a careful selection of the cases to whom this form of treatment may be administered. Improved nursing care for patients given malarial inoculation is important as a means of lowering present mortality records. Favorable results after the use of this form of therapy may not be seen for several months.

III.

EXPERIENCES WITH MALARIAL INOCULATION IN SYPHILIS

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I will not attempt to give you any statistical study of the cases which I have had under my observation, for it would be in large part a duplication of the figures which have been presented to you by the previous speakers. I think there is a remarkable concordance of results throughout the world with respect to malarial treatment of paresis and of tabes dorsalis.

With regard to paresis it would seem that in about one-third of the cases there is a complete remission, and in one-third more a very considerable benefit, and one-third unimproved. And these figures seem to be corroborated by reports from various parts of the world. I will perhaps with your permission, content myself with reference to a few cases of special interest.

The number of cases under the observation of Dr. Greenbaum and myself is considerably less than that of the previous speakers. We treated nearly seventy cases, and this included paresis, tabes dorsalis, cerebrospinal syphilis, and a few cases of congenital syphilis in adults. One case of a paretic, thirty-five years of age, private patient, who had classic serologic and clinical evidence of the disease is of interest. He went through fifteen paroxysms of malaria. Before the treatment was instituted he was violently manical, had to be restrained hand and foot in bed.

At the end of the malaria treatment he was perfectly rational, and after his convalescence left the hospital for his home elsewhere, and for the past two years has been pursuing his usual vocation as a civil engineer giving entire satisfaction. One year after the treatment there was complete negativity of the blood Wassermann which is quite an achievement, because, as Dr. Kirby has remarked, the blood Wassermann and the spinal fluid Wassermann are ordinarily irreducible with the ordinary methods of treatment. His spinal fluid Wassermann was moderately positive, a typical paretic gold curve had changed to a luetic gold curve. A second case is somewhat unique as far as I can make out from the literature. A man of fifty-six with a chronic cerebrospinal lues, fixed pupils and strongly positive blood Wassermann and strongly positive spinal fluid findings sustained upon very slight provocation a fracture of a metatarsal bone of the foot, which did not heal. Later decalcification of the surrounding bones developed which was thoroughly studied by a number of orthopedists. Numerous roentgenograms were taken and it was finally pronounced that he was suffering from an arthropathy. This lasted for some months. He had previously had all sorts of approved luetic treatment.

In view of the fact that he had had so much treatment without influencing his serologic findings, I recommended the use of malarial inoculation. He went through a very nice course of malaria and within a very short time the fracture healed; he was able to walk first with a cane, and later without a cane, whereas, at the time of the first visit he was on crutches; subsequent X-ray pictures of his foot showed a complete recalcification, a complete restoration of structure; the orthopedists now state that it is impossible to differentiate between the bones of the two feet.

This case is of particular interest I think because it suggests the advisability of the use of this method of treatment in early syphilitic arthropathies.

The third case is that of a man thirty-four years of age who had had quite an adequate early treatment for his

syphilis, but his blood Wassermann remained strongly positive. Spinal fluid Wassermann showed a strong positivity with a suggestive paretic curve; in view of this fact we subjected him to malarial inoculation. He went through a course of some twelve or thirteen paroxysms. After that his neurasthenic condition and his loss of sexual power improved, and he took on some twenty pounds in weight. I think my colleagues of this evening, if they were to dwell on this subject would inform you there is often a marvelous improvement in the well-being of paretic patients and others after malarial treatment.

This improved condition was maintained for a year. At the present time he has a strongly positive spinal fluid, a very weakly positive blood Wassermann, and a suggestively paretic gold curve. There are no mental symptoms whatsoever to-day. His neurasthenic symptoms have disappeared. He contemplates marriage and wants our advice upon the subject. Here is a man who, it seems to me, it is advisable to reinoculate with malaria if we can. This brings up the question of the indications for the employment of malarial inoculation. In advanced paresis after a very considerable degree of degeneration has taken place, it is obvious that all one can hope for is improvement, perhaps arrest; in many cases no improvement whatsoever will be achieved.

The most ideal results should be achieved in the early cases of paresis, or preferably, in the pre-paretic state. In those cases in which a patient after an adequate antisyphilitic treatment shows a persistently positive spinal fluid Wassermann and other pathological alterations in the fluid, malarial inoculation should be tried.

Some two years ago I had the opportunity while in Vienna of being shown by the late Professor Kyrle a series of records of patients whom he had treated with malaria, patients in all stages of syphilis. He was treating early syphilis as well as late syphilis, treating it even in the early primary stage after a preliminary course of six neosalvarsan injections, and the treatment followed by six

neosalvarsan injections. He told me that he could count the relapses upon the fingers of one hand and his series of cases covered fifteen hundred inoculations.

Now, the significant thing about his records was this (and he showed them to me at random): Patients who had had persistently positive spinal fluid Wassermanns, more or less latent cases, that had received all sorts of approved luetic treatment, without any change in the serologic findings would show negative reactions in the spinal fluid in from six to nine months after malarial treatment in a very high percentage of cases. This was quite striking, and it is the opinion to-day of some of the best German syphilographers, that malarial inoculation should be employed in this very condition in patients who, after energetic courses of antisyphilitic treatment, show persistently positive spinal fluid Wassermanns, before any nerve symptoms develop. That is the ideal stage in which to treat these patients, for in the majority of cases they are still relatively young men, and fairly robust, and the risk of malaria in such cases is less than in the well advanced cases of paresis.

Now, there is a certain risk with malarial treatment, as has been emphasized by the previous speakers. Some men have been more fortunate than others with their cases. The fatality depends a good bit on selection. In our seventy cases we were fortunate enough to have only one death and that was in a paretic. But a great many of our patients were not paretics. And furthermore none of them were asylum cases, although some quite well advanced.

Again, when you come to treat private patients with malaria you will find that it is a most disturbing and distressing method of treatment to apply. The hardened, lowest stratum of asylum cases may perhaps not complain of suffering, but when you get more sensitive patients who have been bred in greater luxury, you will find that the high fever, the severe chills, the drenching sweats, the accentuation of all previously existing pains and the development of new ones will be bitterly complained of, and it

is not a method of therapy to be lightly taken up, apart from any danger that may be attached thereto.

Now, as has been stated, there is no constant parallelism between the serologic and the clinical improvement. In some you will get a negative blood Wassermann, and spinal fluid Wassermann with little clinical improvement and in other cases quite the reverse may take place. What is most significant of all is the marked regression in the pathologic picture as has been commented upon by Dr. Kirby. Nearly all of the histologists who have examined the brains of paretics who have received malarial treatment are in accord that there is a remarkable change in the microscopic picture to such an extent in many cases that it would be impossible to identify the brains as those of a paretic, and indeed it is quite astonishing to histologists that such a degree of pathologic regression or restoration can take place; even more significant is the fact that in the vast majority of cases in which an opportunity has been given to examine the brain carefully for spirochætes after malarial inoculation they have been found absent. I believe it is generally held that in about 33 per cent. of brains of paretics it is impossible to find spirochætes. But a competent histologist will find them in the remaining cases.

Bielchowsky, Kirchbaum of Hamberg, two observers from Vienna, Straussler and Koskinas, and more recently, Freeman of Washington, have in the aggregate examined almost one hundred brains most carefully and in not a single instance were they able to find spirochætes. Forster of Germany, however, in examining several cases did find spirochætes in one instance.

A very interesting case was related by Jahnel of Munich who did a cerebral puncture upon a case of paresis and found numerous spirochætes. The patient then developed a purulent pleuritis and ran a high temperature for several weeks, finally succumbing. A most painstaking study of the brain failed to reveal spirochætes. This observation has almost the force of an experiment.

Now, the very interesting point has arisen and was touched upon by Dr. Stone, as to the therapeutic mechanism of malarial inoculation in paresis. From the time of Hippocrates and Galen down to Boerhave and Sydenham through to the present time, there have been instances of patients suffering from various psychoses that were improved or arrested through some intercurrent febrile disease. It was a review of this literature that started Wagner-Jauregg upon his fever inducing experiments.

It will be realized that there was no particular specificity in the fevers, but various fevers brought about these results. I should state that the dominant opinion held today chiefly by European observers is that the fever induced is not the prime cause of improvement. Many hold the view that in some way malaria brings about certain antibody production which is noxious to the spirochætes. Others hold that the death of the malarial parasites produces some protein substance which stimulates the defensive mechanism of the body.

We have endeavored in our Research Institute to carry out certain experiments with a view to shedding light if possible upon this very complex question. We have been able to prevent syphilis in the rabbit by giving the rabbit a series of daily very hot baths, four days after intratesticular inoculation of a spirochætic emulsion.

I may add that in some 5,000 syphilitic inoculations in rabbits, as I recall, we have had 100 per cent. successes in inducing syphilis. If these animals receive a hot bath, 113° Fahrenheit for about fifteen minutes on eleven successive days no syphilis develops, no clinical evidence of syphilis, no syphiloma of the testicle, and furthermore if the femoral and popliteal glands are removed several months later and inoculated into other rabbits, which is a necessary procedure to prove failure of infection, these inoculations are negative.

We were enabled too to produce a rapid healing of a secondary syphiloma with fifteen baths, almost daily, excluding Sundays, and with an average rise of temperature

in the rabbit of from 4° to 5° Fahrenheit. Chancres heal as quickly as if you had given them a curative dose of arsphenamine. The spirochætes disappear within a few days. It is quite striking to note the rapidity with which these chancres heal up under hot baths.

Now, of course, this simply shows that the elevation of the body temperature of the rabbit has a healing effect upon rabbit syphilis. It does not indicate whether the effect of the heat is direct or indirect. In order to throw some light upon this question we subjected spirochætes suspended in physiologic salt solution in a test tube to heating upon a water bath.

We carried out three separate experiments of this kind now covering a period of a year and a half or more. In the first experiment, the spirochætes heated to 40° or 41° Centigrade, about 104° to 106° Fahrenheit, for an hour and a half failed to induce syphilis in the rabbit, although at the time of inoculation the suspension under the dark field microscope showed numerously active organisms. They were in some way biologically damaged or paralyzed so they were later unable to produce their disease effect.

In a second series of experiments we did not obtain exactly the same result, but a very interesting one. A series of some twelve rabbits was inoculated and twelve kept as controls. That is, they were inoculated with the unheated spirochætes. The latter all developed syphilis within eighteen to thirty-six days, that is, developed a syphiloma of the testicle containing spirochætes.

But those infected with heated spirochætes within thirty-six days were entirely free, but thereafter from the thirty-sixth day to the eighty-eighth day they began gradually to develop a syphiloma with the presence of spirochætes. Two of them developed the lesion upon the eighty-eighth day. In this experiment the period of incubation was greatly lengthened.

In a third experiment which is about terminating we confirmed the first one. In other words, the animals have

not developed syphilis during an observation period of over one hundred days. Certain precautions are necessary in this experiment. One must not have any large particles of testicle in the spirochætic emulsion because it may not be permeated by the degree of heat employed. One must not pour from the test tube, but pipet the solution out with a pipet because the upper wall of the test tube may contain spirochætes clinging to it which are not subjected to the degree of heat which is registered by the thermometer. I may say the gland transplantations from these rabbits have likewise remained negative.

It would seem from this experiment and from certain others that have been carried out that the spirochæte is extremely thermolabile. If you heat the spirochæte to 105¾° Fahrenheit, for six hours, its motility begins to cease and it breaks up. This is a much lower degree of heat than is necessary to destroy ordinary bacteria.

These rather interesting experiments upon the rabbit suggested to us the trial of very hot baths in the treatment of human syphilis.

It is rather interesting to observe that in almost all countries, patients for some centuries suffering from syphilis have migrated to thermal springs. We have our own hot springs here in the United States. In Japan they have some noted springs at Kusatsu where the natural temperature of the water is extremely high and patients there get into water at a temperature of 121° to 123°; after becoming accustomed to it they can stand this temperature for a few minutes; it is said that these springs are particularly curative for patients who are losing their noses, which suggests to most of us syphilis.

We have been able to produce a temperature from 102° to 103° to 106°, in human beings by means of hot baths without any material danger. The patient has an ice cap upon his head and special appliances are employed to keep the temperature at a given point. The temperature of the water is about 112° or 113° increased gradually; the

maximum temperature is only maintained for fifteen minutes, although the patient is in the water for about forty-five minutes.

We have treated early syphilis by this method in order to determine what it would do. We have noticed the disappearance of the secondary eruption. We observed the disappearance of superficial tertiary eruptions. We have observed a quantitative reduction in the strength of the Wassermann reaction upon which we would not insist too much.

One would hardly expect the use of hot baths by raising the body temperature in the human being to have the same curative influence on syphilis as malaria. It is not our expectation that such would be the case. But we are endeavoring to determine whether the use of extremely hot water associated with other methods may not abbreviate the period of disappearance of symptoms and bring about negativity of the Wassermann test more rapidly and thus constitute an adjunct or aid in the treatment of syphilis. We observed some side effects which were rather interesting. There is a brief leukocytosis followed by a reduction in the white cells, a slight rise in the systolic blood pressure with a marked fall in the diastolic blood pressure, almost to zero at times. There is, on the average, a 10 per cent. increase in the blood sugar and a 10 per cent. decrease in the cholesterol. The uric acid and urea of the blood are unchanged. There is no change in the proteolytic or lipolytic enzymes in the blood.

Whether this method of treatment will have any place in the therapy of syphilis is a question which can only be determined by further observations and study, and whether any other fever inducing method will serve to act as a substitute for malaria can only be determined by further study. The intravenous injection of typhoid vaccine by bringing about a sharp rise of temperature to a very considerable height has given interesting results, but unfortunately the period of fever is not sufficiently protracted.

In malaria we have a rise of temperature of very considerable degree for a period often of six hours continuously, whereas with the injection of foreign proteins or drugs designed to raise the body temperature the rise of temperature is very brief. That must be taken into consideration in adopting substitute methods. There can be no doubt, I believe, and it is the general consensus of opinion, that the results achieved from malarial inoculation in paresis have exceeded those which have been obtained by other methods. Paresis was the one stumbling block in the progress of our treatment of syphilis. Various remarkable advances had been made but despite all these advances, despite the introduction of the newer drugs, paresis was still the malign and ultimate outcome in many cases.

But it does seem now as if methods are at hand whereby paresis may be improved, may be perhaps arrested, and who knows, may be cured. If we may judge from the remarkable change in the microscopic picture and if we may judge from the fact that in Vienna some of the paretic patients are well and working after six, seven or eight years, and some of Dr. Kirby's cases are apparently well and working at the end of three or four years, it is only the future which will enlighten us as to the ultimate verdict.